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Chronic Hepatitis

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Chronic hepatitis, the primary cause of liver failure and hepatocellular carcinoma, affects millions of adults and children worldwide. The 2 most common causes, viral hepatitis B and C, alone affect millions of children and significantly contribute to the morbidity and mortality of the populations affected. Autoimmune hepatitis (AIH), one of the most common global noninfectious causes of chronic hepatitis, is less frequent than the infectious hepatidities. However, its global occurrence and significant impact on children's health makes autoimmune hepatitis important for pediatric hepatologists. The evaluation, monitoring, and treatment of these chronic conditions are challenging. Caring for children with these conditions is further complicated by limited data and therapies in this group, and concerns for the child's growth and development as they relate to both disease and therapy.

In this report, a cadre of international experts in pediatric hepatology highlight leading issues in the field. We provide consensus recommendations based on available literature, and expert opinion as appropriate, for the care of children with hepatitis B and C and autoimmune hepatitis regardless of their country of residence. We also identify areas for future research that we hope will serve as a catalyst to advance our understanding and treatment of these conditions.

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CURRENT CONTROVERSIES AND IMPORTANT ISSUES

Hepatitis B

Whom to Treat

Because a consensus on guidelines for the treatment of chronic hepatitis B in children has not been established, current indications for therapy in adults with chronic hepatitis B virus (HBV) infection also are applied for children (1). Theoretically, treatment with an ideal antiviral agent should be given as early in life as possible to interrupt viral replication and potential liver damage with chronic infection, and it is suggested that all children with chronic HBV should be considered for treatment. Factors that are predictive for a positive response to currently available therapies, however, include high pretreatment levels of aminotransferase, low pretreatment HBV DNA levels, late acquisition of HBV infection, and higher hepatocellular inflammation. Whether patients with an alanine aminotransferase (ALT) level of less than 2 × the upper limit of normal (ULN) should be treated is awaiting further investigation. Available information suggests that immune tolerant patients with normal or minimally elevated ALT respond poorly to current therapies (2). Therefore, currently no drug treatment is recommended for this group of patients.

When to Treat

Decisions to treat and the type of treatment require consideration of: hepatitis e antigen (HBeAg) positivity and elevation of HBV DNA ($>10^5$ copies/mL or 20,000 IU/mL for HBeAg-positive patients); histological stage; likelihood of response (increased aminotransferase $>2\times$ ULN); tolerance of treatment-associated side effects; previous treatment and drug resistance; and coexisting infection or disease. Disease activity before and during treatment may be assessed by markers of viral activity (HBV DNA levels and presence of HBeAg) and markers of immune-mediated inflammation (aminotransferase enzymes and histology).

Acute elevation of ALT level $>5\times$ ULN may be followed by spontaneous HBeAg seroconversion. It is therefore reasonable to delay treatment for an observation period of at least 3 months if there is no concern of hepatic decompensation. In patients with signs of hepatic decompensation, non–interferon-based treatment should be started as early as possible. Careful and frequent monitoring for level of consciousness, serum bilirubin, and prothrombin time is recommended. If liver transplantation is an option, then referral to a transplant center is recommended.

How to Treat

The aim of treatment is to reduce the risk of morbidity and mortality from cirrhosis and hepatocellular carcinoma, and to eradicate replicative infection by clearance of HBeAg. The choice of HBV therapy depends largely on patient and viral factors, and availability of the therapy and required monitoring for that therapy. End of treatment usually is defined according to the virological response (VR), which is the absence of HBeAg and undetectable HBV DNA.

Interferon-α (IFN-α). Interferon (IFN) therapy is unlikely to be of benefit in children with perinatally acquired infection who have normal or minimally elevated aminotransferases (3). Predictors of IFN response include (4) active hepatitis; low HBV DNA levels (<1000 pg/mL); high serum aminotransferase enzymes ($>2\times$ ULN); short duration of disease; non-Asian ethnic origin; and horizontal transmission.

The recommended treatment regimen for IFN-α is 5 to 10 MU/m^2 3 times weekly by subcutaneous injection for 4 to 6 months. The response rates vary, depending on route of acquisition, disease activity, and treatment. Adult data suggest that HBeAg-negative chronic disease should be treated for 12 months, whereas another study demonstrates that longer duration of 24 months increased sustained response rates (5). Pretreatment with corticosteroids (“priming”) and their withdrawal before commencing IFN-α may exacerbate the host immune response, facilitating seroconversion (6). The benefit, however, remains unproven (7), and is associated with the risk of precipitating fulminant liver failure.

A meta-analysis of 240 children in Europe demonstrated that IFN-α treatment increased the likelihood of both HBV DNA and HBeAg clearance (odds ratio [OR] 2.2) compared with untreated controls, although overall clearance of HBeAg was only 30% compared with 10% for controls (8). IFN is the only effective therapy for chronic hepatitis D, requiring high doses (9 MU for 12 months) with high relapse rates (9).

IFN is limited by its adverse side effects. Fever, flulike symptoms, and bone marrow suppression may occur. Autoimmune thyroid disease, alopecia, emotional disturbances including severe depression, and retinal changes also are important side effects.

Pegylated Interferon (PEG-IFN). The covalent attachment of a polyethylene glycol (PEG) moiety to IFN-α enhances its half life and removes its immunogenicity leading to once-weekly rather than thrice-weekly injections. In adults, the combination of PEG-IFN (180 μg weekly) and Lamivudine 100 mg daily for 48 weeks produced greater viral suppression, but no real difference in seroconversion rates (10). There are a few small studies to date of PEG-IFN in children with HBV with or without lamivudine, but the results are inconclusive.

Lamivudine. Lamivudine is a pyrimidine nucleoside analog that prevents replication of HBV in infected hepatocytes. It leads to a rapid reduction in plasma HBV DNA load, with 97% reduction within 2 weeks of commencing treatment, and undetectable levels within 4 weeks, which is sustained during treatment (11). The American Association for the Study of Liver Diseases (AASLD) has defined categories of response to antiviral therapy (Table 1). These categories also have useful application to children.

Lamivudine is well tolerated, with a dose of $3\,\text{mg}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$ (maximum = 100 mg) providing levels of exposure and trough concentrations similar to those in adults receiving 100 mg (12). An international, randomized, double-blind, placebo-controlled trial of 286 children with chronic HBV showed a complete response (HBeAg clearance and undetectable HBV DNA after 52 weeks of treatment) in 23% compared with 13% placebo (2). In those with ALT $>2\times$ ULN, response rates were 34% and 16%, respectively. Drug-resistant YMDD variants emerged in 18%.

The optimal length of time to achieve VR with lamivudine has not been defined. The durability of the VR following treatment also has not been extensively evaluated in children. Some studies recommend a duration of 36 months of treatment until VR is achieved, with or without seroconversion (13). Others suggest that the

TABLE 1. *Definition of response to antiviral therapy of chronic hepatitis B*

Category of response	
Biochemical (BR)	Decrease in ALT to normal level
Virological (VR)	Loss of HBeAg and undetectable HBV DNA levels
Primary nonresponse	(Not applicable to interferon therapy) No decrease in serum HBV DNA by <2 log 10 IU/mL after at least 24 wk of therapy
Virological relapse	Increase in serum HBV DNA of 1 log 10 IU/mL after cessation of treatment in ≥2 tests >4 wk apart
Histological response (HR)	Decrease in histology activity index by ≥2 points and no worsening of fibrosis score compared with pretreatment liver biopsy
Complete (CR)	Fulfill criteria of BR, VR, and loss of HBeAg
Time of assessment	
On therapy	During therapy
Maintained	Throughout the course of treatment
End of treatment	At end of defined course of therapy
Off therapy	After ending treatment
Sustained (SR-6)	6 mo after cessation of treatment
Sustained (SR-12)	12 mo after cessation of treatment

ALT = alanine aminotransferase; HBeAg = hepatitis e antigen; HBV = hepatitis B virus.
Modified from the 2007 American Association for the Study of Liver Diseases HBV guidelines, *Hepatology* 2007:45;507–39.

necessary duration of treatment with lamivudine seems to be at least 1 year with recommendations to continue treatment for 6 months after HBeAg seroconversion (14). Long-term lamivudine treatment (>3 years) did not significantly increase seroconversion rates, and there was a higher incidence of viral resistance (13). Lamivudine should be discontinued once YMDD mutants have emerged (13), especially in the setting of ongoing transaminases elevation.

HBeAg status, ALT levels, and HBV DNA are used to monitor therapy and to predict the emergence of mutants. Recent reports suggest that serum HBV RNA levels also may be useful in monitoring patients undergoing therapy with lamivudine (15).

Lamivudine has limitations. Resistance to lamivudine may occur because of a specific HBV mutation (tyrosine-methionine-aspartate-aspartate or YMDD mutation) in the polymerase gene. The mutant virus may revert to wild type after lamivudine therapy is withdrawn and rebound to pretreatment levels.

Adefovir. Adefovir is a purine analog that inhibits viral replication, and also may augment natural killer-cell activity and endogenous IFN activity. HBV strains resistant to lamivudine are susceptible to adefovir.

A recent randomized controlled trial (15a) suggests that adefovir is effective in 23% of children older than 12 years, which is similar to adults, and less effective in younger children with little difference in efficacy compared with placebo. Viral resistance did not occur in the study, but is reported in adults in 1% at 1 year, rising to 29% at 5 years. It is treated by combination therapy with lamivudine, but there is increased resistance to adefovir in patients with resistance to lamivudine.

How to Monitor the Child With Chronic HBV

The natural history of hepatitis B in children is complex and long-term data are unavailable. As a result, definition of appropriate guidelines for management has been difficult. There are also varying environmental effects of the virus in different parts of the world, which further complicate clinical management.

Current recommendations by the AASLD (16) for monitoring HBV infections include the following:

1. HBeAg-positive and -negative patients who meet the criteria for chronic HBV should be treated
2. HBeAg-positive patients with persistently normal ALT should be tested for ALT elevations every 3 to 6 months with HBV DNA testing if the ALT becomes elevated. HBeAg status should be checked at 6 monthly intervals
3. Those patients with persistently elevated ALT levels $>2 \times$ ULN and HBV DNA 20,000 IU/mL should be considered for treatment
4. HBeAg-negative patients with normal ALT and HBV DNA <2000 IU/mL should be tested for ALT elevations every 6 to 12 months
5. ALT and HBV DNA monitoring should be more frequent when ALT levels remain elevated

Liver biopsy is not mandatory for treatment, but may be recommended to assess the necroinflammatory grade and the fibrotic stage, and to exclude other etiologies of elevated ALT levels.

Hepatocellular carcinoma (HCC) has been reported in children with chronic HBV (17,18), but rarely occurs in the first decade of life. Many clinicians obtain serum α-fetoproteins at 6 monthly intervals with annual abdominal ultrasounds for surveillance. Much of this

screening, however, is done with legal concerns because there are no data that suggest that such screening is cost effective or that it may alter the natural course of disease. Predictors of future risk of cirrhosis or HCC need to be better defined to help with screening patients for HCC. This may be particularly relevant when there is advanced fibrosis or a family history of hepatic cancer.

Consensus Recommendations for HBV

1. Children 2 to 17 years of age who are HBsAg seropositive for more than 6 months, and have evidence of active viral replication (positive HBeAg, HBV DNA levels $>10^5$ copies/mL or 20,000 IU/mL in their serum) for more than 6 months, should be considered for therapy
2. Treatment with IFN, or lamivudine in children older than 2 years, should be considered; currently, children under 12 years should not be treated with adefovir
3. Monitoring HBV infections should be done according to the AASLD guidelines

Interferon Therapy: Recommendations. Based on European experience, consensus recommendations, based on short-term efficacy, are as follows (19): to accelerate HBeAg clearance in a subgroup of patients, selection of children with HBeAg and HBV DNA positivity, with low to intermediate HBV DNA levels and abnormal aminotransferase enzymes, ages 2 years or older; contraindicated in children with decompensated liver disease, cytopenia, severe renal or cardiac disorder, and autoimmune disease; the standard treatment regimen is $5\,mU/m^2$ 3 times per week for 6 months. Retreatment in nonresponders is not indicated.

Lamivudine Therapy: Recommendations. To accelerate HBeAg clearance in a subgroup of patients, selection of children with HBeAg and HBV DNA positivity, with low to intermediate HBV DNA levels and abnormal aminotransferase enzymes, ages 2 years or more; the standard treatment regimen is $3\,mg \cdot kg^{-1} \cdot day^{-1}$ (maximum 100 mg) for 12 months. Prolonged treatment in nonresponders is not currently indicated.

Hepatitis C

We know little about the natural history of hepatitis C virus (HCV) infection in children or about the risk factors associated with progression of liver disease in this population. Therefore, the issue of treating children with chronic HCV infection is challenging.

Whom to Treat

Given the generally indolent course of HCV infection in children (20–22) and the efficacy and safety profile of available therapies, a reasonable approach is to offer treatment only to children with evidence of liver disease. However, progressive liver disease, including cirrhosis necessitating liver replacement and HCC, has been reported during childhood (23,24). Eradicating HCV to avert these potential complications in later life, as well as to eliminate the social stigma associated with harboring a contagious infection, is a justifiable reason to pursue antiviral therapy in children. Therefore, it may be argued that all children with detectable serum HCV RNA for longer than 6 months, regardless of degree of liver injury, should be considered treatment candidates, particularly if such is administered in the context of a clinical trial. Preemptively treating HCV-infected children who are being considered for stem cell or solid organ transplantation, or those with underlying hematological and renal disease, is especially controversial. The decision to treat or not treat these usually complex patients should be made based on individual benefits and risks.

When to Treat

The reported spontaneous viral clearance rate in children varies considerably from 0% to 45% (25,26), and little is known about the virological and host factors involved in this process. Therefore, it is difficult to formulate firm recommendations about when to initiate treatment. In children with vertically acquired HCV, seroconversion is unlikely to occur after early childhood (26), and it seems prudent to wait until then before offering treatment, unless significant liver dysfunction occurs earlier.

How to Treat

Sustained virological response (SVR), defined by undetectable serum HCV RNA 24 weeks after completion of therapy, correlates with regression of liver fibrosis; reduced rates of HCC, hepatic failure, and liver-related deaths; and improved quality of life in adults. Therefore, achieving SVR is the primary treatment goal.

INF and Ribavirin. In a large review of pediatric IFN monotherapy trials, SVR occurred in 27% and 71% of those infected with HCV genotype 1 and HCV genotypes 2 or 3, respectively (27). The addition of ribavirin to IFN-based regimens results in enhanced rates of SVR in adults with HCV (28). In children, the aggregate reported SVR with combination treatment is 44% and 89% for those infected with HCV genotype 1 and HCV genotypes 2 or 3, respectively (29). To date, IFN plus ribavirin is the only

licensed therapy for children with HCV in the United States.

PEG-IFN. Several randomized clinical trials in adults verified considerably better SVR rates with PEG-IFN, particularly when given with ribavirin, compared with IFN (30). To date, only 2 small trials have assessed PEG-IFN in children with chronic HCV infection (31,32). In contrast to the results in adults, SVR rates appear to be similar between children treated with IFN products alone or with ribavirin. Ongoing trials comparing PEG-IFN alone or with ribavirin (PEDS-C clinical trial) will better define optimal treatment in children with HCV (31).

SVR is unlikely to occur in patients with detectable HCV RNA after 24 weeks of treatment (32,33); consequently, stopping therapy is recommended under these circumstances. In contrast to adult data, no pediatric-specific data assess treatment duration based on infecting HCV genotype.

Treatment of Prior Treatment Nonresponder and Relapsers

Retreatment with PEG-IFN and ribavirin results in SVR in 40% and 10% of adults who fail to respond to PEG-IFN alone and PEG-IFN plus ribavirin, respectively. Similarly, up to 50% of adults who relapse after IFN monotherapy achieve SVR after retreatment with PEG-IFN plus ribavirin combination. Positive predictors of SVR include HCV genotype 2 or 3 infection and low pretreatment viral load (34,35). Retreatment in adults may reduce liver inflammation and fibrosis progression, and possibly reverse early cirrhosis. If confirmed, these benefits may translate into delay in HCC development (36). Little is known about retreating pediatric nonresponders and relapsers.

Criteria for Performing Liver Biopsies

The need for and timing of a liver biopsy in children with HCV infection is debatable (37). A liver biopsy may be particularly useful to assess degree of liver injury and exclude potential concurrent diseases, particularly in children with normal liver tests who are being considered for antiviral therapy. However, even in this setting the liver biopsy is controversial for those with HCV genotype 2 and 3 infections whose SVR rates exceed 80% (33,38). Less invasive tests, such as the use of serological markers of fibrosis and transient elastography, appear promising in adults (39,40) but have not been tested in children.

Consensus Recommendations for HCV

1. Children with detectable serum HCV RNA and evidence of active inflammation on biopsy should be considered for antiviral treatment. However, children with no biochemical and mild histological abnormalities and those with underlying comorbidities should be considered for treatment on an individual basis, particularly if such is administered in the context of a clinical trial.
2. Treatment should consist of 48 weeks of IFN plus ribavirin for those with undetectable HCV RNA by 24 weeks of therapy. Therapy should be stopped for those with detectable HCV RNA at 24 weeks of therapy.
3. Treatment-naïve children and nonresponders and relapsers to IFN-based treatment should be considered for PEG-IFN therapy in the context of a clinical trial. The issue of PEG-IFN with or without ribavirin replacing IFN plus ribavirin awaits completion of current ongoing clinical trials.
4. Children undergoing treatment need to be carefully monitored for adverse events, particularly hematological abnormalities, weight loss, and depression. Treatment should be prescribed and supervised only by experienced health care providers.
5. Children who are considered treatment candidates should preferably undergo liver biopsy.

AIH

Diagnostic Criteria for AIH and Variant Conditions

Diagnosis of AIH is based on a series of positive and negative criteria (41). Liver biopsy is necessary to establish the diagnosis, the typical histological picture including: a dense mononuclear and plasma cell infiltration of the portal areas, which expands into the liver lobule; destruction of the hepatocytes at the periphery of the lobule with erosion of the limiting plate (''interface hepatitis''); connective tissue collapse resulting from hepatocytes death and expanding from the portal area into the lobule (''bridging collapse''); and hepatic regeneration with ''rosette'' formation. In addition to the typical histology, other positive criteria include elevated serum aminotransferases and immunoglobulin (Ig) G levels, and presence of anti-nuclear antibodies, anti-smooth muscle antibodies (1:20), or anti-liver and kidney microsomal antibodies-1 (1:10). The diagnosis of AIH has been advanced by the criteria developed by the International Autoimmune Hepatitis Group (42), in which negative criteria are taken into account in addition to the positive criteria mentioned above. The group has provided a scoring system for the diagnosis of AIH, mainly used for research purposes (42). Other autoantibodies less commonly tested but of diagnostic importance include those to liver cytosol type 1, anti-neutrophil cytoplasm, and soluble liver antigen (Table 2).

In pediatrics, primary sclerosing cholangitis is frequently characterized by features similar to autoimmune

TABLE 2. *Antibody profiles of autoimmune hepatitis type 1 and 2*

Antibody	Type 1 AIH	Type 2 AIH
IgG	Elevated	Elevated
ANA	1:20	—
αSMA	1:20	—
αLKM-1	—	1:10
αLC-1	—	Detectable
pANNA	Detectable	—
αSLA	±	±

AIH = autoimmune hepatitis; Ig = immunoglobulin; ANA = antinuclear antibody; SMA = smooth muscle antibody; LKM = liver and kidney microsomal antibody; LC = liver cytosol; pANNA = peripheral anti-neutrophil nuclear antibody; SLA = soluble liver antigen.

hepatitis, including elevated titers of autoantibodies, in particular antinuclear and smooth muscle antibodies, elevated IgG, and interface hepatitis (43). Because these features are shared with AIH, in the absence of cholangiographic studies at presentation many of these children are diagnosed and treated as AIH, although the diagnosis of sclerosing cholangitis may become apparent during follow-up. This condition is increasingly referred to as autoimmune sclerosing cholangitis and responds satisfactorily to immunosuppression, at least in regards to the parenchymal inflammation, if treatment is started early.

When to Treat

The decision to treat is based on the presence of symptoms, serum aminotransferase elevation typically with elevated serum IgG, and histological evidence of the typical chronic active hepatitis. The goal of therapy is to reduce or eliminate the inflammation within the liver, to induce remission, to improve symptoms, and to prolong survival (44–46). Although cirrhosis is found between 44% and 80% of the time at diagnosis in children with AIH (47,48), mortality is low and most children remain clinically stable, with a good quality of life during long-term treatment.

How to Treat

Treatments used for AIH include prednisone alone, combination therapy with prednisone and azathioprine, azathioprine alone, cyclosporine, and other immunosuppressants. These have achieved remission in nearly 80% of children with AIH. In contrast, onset at an early age, acute presentation, hyperbilirubinemia, and presence of HLA DRB1∗03 are predictive of a poor response to corticosteroid treatment (49).

Remission is defined by complete clinical, biochemical, and histological resolution of inflammation. The histological response lags behind the biochemical response, and clinical remission does not necessarily mean that there is histological evidence of resolution. Histological response is characterized by a significant reduction of necroinflammatory activity in the liver, which occurs after clinical and biochemical response (50–53). Rodrigues et al (50) found an improvement of portal inflammation intensity in 95% of cases after treatment. Relapse is characterized by increase of serum aminotransferases levels after remission has been achieved. Nonadherence to medications is an important risk factor for poor outcome in children with autoimmune hepatitis (55).

The optimal duration of immunosuppressant treatment for AIH is not clear. Even though treatment may be discontinued after a sustained remission for at least 2 years and a normalized liver biopsy, relapse is common and experience has shown that most pediatric patients with AIH require long-term treatment (48).

Prednisone Plus Azathioprine. Conventional therapy utilizes both prednisone and azathioprine. Prednisone is initially dosed at 2 mg/kg per day, with a maximum dose of 40 to 60 mg/day. The dose is gradually decreased over a period of 4 to 8 weeks, to a maintenance dose of 2.5 to 5 mg/day (56). In most patients, an 80% decrease in the aminotransferase levels is achieved in the first 2 months, but their complete normalization may take several months (56,57). Azathioprine is added at a dose of 0.5 to $2\,\mathrm{mg}\cdot\mathrm{kg}^{-1}\cdot\mathrm{day}^{-1}$, several weeks into prednisone treatment and after the serum aminotransferase levels begin to decrease (54). Measurement of thiopurine methyltransferase activity level before initiating azathioprine therapy is advised so that its metabolism can be anticipated (57). Azathioprine may be added to treatment from the beginning, but caution is important because of its potential hepatotoxicity.

Cyclosporine. Cyclosporine has been used effectively in adults and children to induce remission. Monotherapy with cyclosporine is classically used for 6 months, followed by the addition of prednisone and azathioprine; 1 month later the cyclosporine is discontinued (58). The recommended dose of cyclosporine is $4\,\mathrm{mg}\cdot\mathrm{kg}^{-1}\cdot\mathrm{day}^{-1}$ in 3 divided doses, increased if necessary every 2 to 3 days to achieve a whole blood concentration of 250 ± 50 ng/mL for 3 months. If there is clinical and biochemical response in the first months, the cyclosporine is reduce to achieve a concentration of 200 ± 50 ng/mL for the following 3 months.

Other Treatments. Limited data are available regarding the use of tacrolimus, methotrexate, cyclophosphamide, budesonide, mycophenolate mofetil, and ursodeoxycholic acid. Low-dose tacrolimus has been shown to ameliorate liver inflammation and fibrosis in steroid refractory autoimmune hepatitis in adults. Mycophenolate mofetil has been used in children in a small group of patients with good results (59). In patients who demonstrate features of

autoimmune sclerosing cholangitis, the addition of ursodeoxycholic acid to the treatment regimen is warranted, although of unproven benefit.

Consensus Recommendations for AIH

1. Liver biopsy is required to establish the diagnosis of AIH.
2. Treatment should commence using prednisone, to which azathioprine or 6-mercaptopurine is added. The prednisone should be weaned as tolerated.
3. Discontinuation of therapy could be considered after 1 to 2 years of complete remission and a normal liver biopsy.

RESEARCH AGENDA

HBV

Areas in need of study include the following:

1. Methods to predict a spontaneous HBeAg seroconversion in children, which will follow the surge of ALT, and may not need therapy
2. The role of α-fetoprotein and/or abdominal ultrasonography in the follow-up testing for children with chronic hepatitis B virus infection
3. The optimal duration of therapy with the newer drugs and regimens
4. The role in pediatrics for new noninvasive monitoring tools
5. Optimal therapy for immune-tolerant and HBeAg-negative patients
6. Role of HBV genotyping in the evaluation and treatment of HBV-infected children

HCV

Future research should

1. Delineate the natural history of HCV infection by systematic assessment of clinical and histological outcomes in children. The primary aim of such analysis should be to uncover virological and host factors involved in the progression of liver disease.
2. Conduct appropriately designed multicenter pediatric trials in tandem with those in adults as newer antivirals emerge.
3. Determine the utility of serological markers and transient elastography in the assessment of liver fibrosis in children. Include children a priori in the study of newer noninvasive tools that assess liver fibrosis.
4. Establish national and international collaborations that will facilitate achieving these ambitious research goals. Therefore, necessary academic, administrative, and financial resources need to be identified and allocated for this important endeavor.

AIH

Future research should

1. Evaluate the efficacy of new immunosuppression agents in the treatment of AIH.
2. Design protocols for the treatment of refractory AIH.
3. Improve treatment of posttransplant de novo and recurrent AIH.
4. Design protocols that investigate the reversibility of cirrhosis in cases of AIH in children and adolescents.
5. Determine the value of azathioprine metabolite measurements in children with autoimmune hepatitis.
6. Continue the study of epidemiology of AIH in different areas of the world: developed, intermediate, and underdeveloped countries.
7. Define the role of viruses such as hepatitis A, hepatitis C, and Epstein-Barr virus in the pathogenesis of AIH.

CONCLUSIONS

Viral hepatitis B and C and autoimmune hepatitis are leading hepatitides that concern pediatric hepatologists around the world, and their prevalence among children globally make them common causes of morbidity and mortality. The ability to diagnose and treat these entities is improving, thereby positively impacting survival. However, despite the advances in our understanding of these conditions and tools for treatment, significant limitations still exist.

In this document, we have summarized the current challenges in pediatric hepatology and made consensus recommendations based on current evidence and expert opinion, which are applicable to patients around the globe. We have further outlined areas for research that we feel will best advance pediatric hepatology in the area of hepatitis. The persistence of pediatric hepatologists around the world in striving for cures for these diseases, and the support of the world's societies of pediatric gastroenterology, hepatology, and nutrition, will help remove these conditions from the possible causes of morbidity for children.

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